

TENIDAP - A NEW ANTIARTHRITIC AGENT

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SUMMARY: Tenidap sodium is a novel cytokine inhibitor. Early studies in RA suggest a disease modifying profile as well as providing symptomatic relief. The drug is also effective in OA at a significantly lower dose. The results of clinical trials in RA and OA, which address efficacy and safety, are awaited with interest.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) continue to provide pain relief and suppression of inflammation to patients with arthritis. Despite this, there is no evidence that NSAIDs alter disease outcome in the major inflammatory forms of arthritis such as rheumatoid disease. The search for new antiarthritic agents has led to the development of tenidap sodium (Pfizer-Groton).

PHARMACOLOGY

Although tenidap inhibits cyclooxygenase, a property it shares with NSAIDs, it also interferes with 5-lipoxygenase - the enzyme which converts arachidonic acid to 5-hydroperoxy eicosatetraenoic acid (5-HPETE) which is then converted to leukotrienes (1,2). Tenidap inhibits both of these enzymes in cultures of rat basophilic leukaemia cells stimulated with a calcium ionophore (4) and also inhibits the production of both enzymes in synovial fluid of patients with rheumatoid arthritis (3). These actions have recently been reviewed by Robinson (5). Tenidap has also been shown to inhibit the production of interleukin-1 from murine peritoneal macrophages (6) and the production and activity of IL-1, IL-6 and TNF by monocytes obtained from human peripheral blood (7). Interleukin-1 activity in synovial fluid of patients with rheumatoid arthritis is reduced by tenidap (8) and recently tenidap has been shown to have dose dependent free radical scavenging effects *in vitro* (9).

Tenidap sodium has been shown to inhibit carrageenan induced oedema (1) and to modify phospholipase A2 induced paw oedema in the mouse (10). The drug has been extensively studied in the rat adjuvant arthritis model (11). In this study tenidap was compared with cyclophosphamide and dexamethasone with C-reactive protein concentrations measured as an indication of disease severity. Tenidap and dexamethasone suppressed both the primary and secondary CRP and swelling responses. When treatment was commenced after the secondary adjuvant disease was established, only dexamethasone and tenidap sodium inhibited CRP and swelling. Dexamethasone and cyclophosphamide reduced lymphocyte numbers while tenidap treatment was associated with an increase in lymphocytes, suggesting that this drug had a different mechanism of action.

CLINICAL STUDIES

In a four week trial in patients with rheumatoid arthritis (RA), patients treated with Tenidap demonstrated a significant improvement in the number of painful joints, grip strength, overall assessment and ARA functional capacity (12). In a study of 10 patients with active RA, tenidap (120 mg/day) inhibited LTB₄ production by peripheral blood neutrophils. LTB₄ concentrations were also reduced in synovial fluid obtained from these patients (3). In this short term (seven day) study, improvement also occurred in standard clinical parameters of grip strength, pain and number of tender and swollen joints. Other clinical trials in RA have shown similar results (13) on lipoxygenase production and have also demonstrated a significant and sustained effect of tenidap on serum C-reactive protein (CRP) concentrations (14,15). CRP is one of the recognised markers of inflammatory activity in RA and is not influenced by standard non-steroidal anti-inflammatory drugs. CRP concentrations are, however, reduced by slow acting antirheumatic drugs such as salazopyrin, gold and D-penicillamine (16).

Clinical trials of tenidap are currently being conducted in both RA and osteoarthritis (OA) and the drug has now been given to several thousand patients with RA and OA. There seems little doubt from these preliminary studies that tenidap sodium, with its cytokine modifying activity, is an entirely new type of anti-arthritis preparation. Clinical trial data to provide information on side effect and dose profile is urgently awaited but this drug will make a significant contribution to the management of rheumatic diseases.

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